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Expression of FcεRI on dendritic cell subsets in peripheral blood of patients with atopic dermatitis and allergic asthma

To the Editor:

Allergic disorders are characterized by elevated serum IgE levels. Cross-linking of IgE bound to FcεRI on mast cells and basophils results in release of proinflammatory mediators that mediate an allergic response. Besides mast cells and basophils, which play a role in the effector phase of an allergic response, antigen-presenting cells in humans have also been shown to express FcεRI. Expression of IgE on FcεRI on antigen-presenting cells has been shown to increase the efficiency of antigen presentation and thereby lowers the threshold for allergen uptake. Therefore, FcεRI-expressing dendritic cells might be important in the initiation of allergic responses. In contrast with mast cells and basophils, which express FcεRI consisting of 4 subunits (αβγγ), FcεRI on dendritic cells lacks the signal amplifying β-chain and consists of only 3 subunits.¹ Previous studies have shown FcεRI expression on Langerhans cells in skin of patients with atopic dermatitis (AD)² and on dendritic cells (DCs) in the lung of patients with allergic asthma (AA).³ In a study published in this journal,⁴ an increased FcεRI expression was observed on basophils, myeloid DCs (mDCs), and plasmacytoid DCs (pDCs) in the blood of patients with AA compared with healthy controls (HCs). Recently it was demonstrated that in patients with AD, pDCs can release IL-10 on aggregation of FcεRI.⁵

In the current study, we investigated the expression of FcεRI on basophils, mDCs, and pDCs in the blood of patients with AD and AA and HCs to examine whether these FcεRI-expressing blood DCs are a general finding in allergy or whether it might be disease-specific.

From each patient group and controls, 6 persons were selected. Patients with AD, age 25 to 55 years, were diagnosed according to the criteria of Hanifin and Rajka⁶ and had moderate to severe AD (mean Leicester Sign Score of 44; range, 28-68). Mean serum IgE levels were determined through use of the CAP system (Pharmacia Diagnostics, Uppsala, Sweden), and the mean value was 7387 kU/L (range, 268-27,765 kU/L). As an objective disease parameter for AD,⁷ serum thymus and activation-regulated chemokine (TARC) levels were measured by ELISA. Mean serum TARC levels in the patients with AD

were 5672 pg/mL (range, 954-13,997 pg/mL). Patients with AA, age 28 to 51 years, were diagnosed according to American Thoracic Society criteria⁸ and had mild to severe disease with a mean PC₂₀ (shortened challenge) of 4.84 (range, 0.5-14). The mean serum IgE level was 172 kU/L (range, 50-431 kU/L), and mean serum TARC level was 136 pg/mL (range, 50-265 pg/mL). Patients with AA had no history of AD, and vice versa. Patients did not use systemic immunosuppressive drugs or antihistamines, but the use of topical or inhaled steroids was allowed. As HCs, persons without a history of allergic disorders were included (mean serum IgE, 31 kU/L; mean serum TARC, 164 pg/mL).

PBMCs were isolated from heparinized blood by density gradient centrifugation using Percoll 1.078 (Amersham Biosciences AB, Uppsala, Sweden). Cell-specific markers and FcεRI expression were determined by flow cytometry (FACSCalibur, Becton Dickinson, San Jose, Calif). Data were analyzed using FCSexpress 2 software (DeNovo Software, Thornhill, Ontario, Canada).

Basophils were characterized by high CD123 expression. mDCs were defined as Lineage cocktail 1 (CD3, CD14, CD16, CD19, CD20, CD56; BD Bioscience, San Jose, Calif)-negative and blood dendritic cell antigen 1-positive (CD1c; Miltenyi Biotec, Bergisch Gladbach, Germany). pDCs were defined as lineage-negative and blood dendritic cell antigen 4-positive (Miltenyi Biotec). Between patients and controls, there was no difference in the percentage of pDCs (0.21% ± 0.07% vs 0.31% ± 0.11%) or mDCs (0.51% ± 0.03% vs 0.52% ± 0.13%). Expression of FcεRI was determined using a CRA-1 antibody (clone AER-37, IgG2b), which was a kind gift of Prof Dr C. Ra (Nihon University School of Medicine, Tokyo, Japan). This antibody shows no competition with IgE in binding to FcεRI. As a control, cells were stained with isotype matched control antibodies. Values of their mean fluorescence intensity were subtracted from each value of the appropriate fluorochrome-conjugated antibody.

On basophils, no significant difference in FcεRI expression was seen between the groups (Fig 1, A). Both mDCs and pDCs showed an increased expression of FcεRI in the patients with AD (Fig 1, B and C). On mDCs of patients with AA, a slight increase in FcεRI expression was seen; however, this was not significant. The FcεRI expression on mDCs was correlated with the FcεRI expression on pDCs ($r = 0.775$; $P < .001$; data not shown).

Subsequently, the correlation between serum IgE levels and FcεRI expression was determined. On basophils, no correlation was observed for the FcεRI expression. For lower serum IgE levels, however, a trend to a positive correlation was noted. For both mDCs and pDCs, a correlation was found between FcεRI expression and serum IgE levels ($r = 0.715$ and $r = 0.684$, respectively).

In the current study, we demonstrated that in contrast with patients with AA, mDCs and pDCs of patients with AD express increased levels of FcεRI. These results are in contrast with an earlier published article in which FcεRI expression was increased on mDCs and pDCs in patients

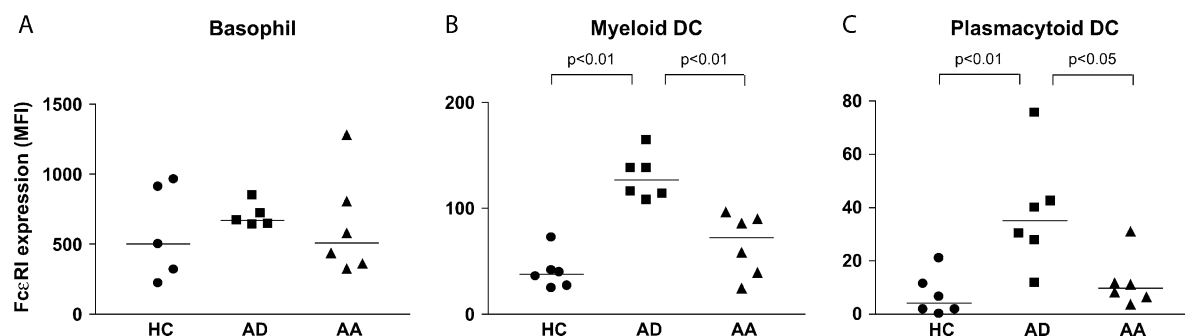


FIG 1. Increased expression of FcεRI on blood myeloid and plasmacytoid DCs from patients with AD. In the blood of HCs and patients with AD and AA, the expression of FcεRI was determined on basophils (A), myeloid DCs (B), and plasmacytoid DCs (C) using flow cytometry. FcεRI expression was determined as mean fluorescence intensity (MFI). Statistical difference was determined by a Mann-Whitney *U* test.

with AA.⁴ Although the mean serum IgE of patients with AA in that study did not differ very much from that of our patients (210 vs 172 kU/L), patients with AA with very high serum IgE are shown in the individual figures. This might indicate that these patients also have AD, because AD is often accompanied by high serum IgE. In our study, patients with AA did not have AD. Because the expression of FcεRI on both DC subsets is correlated with the serum IgE, the low FcεRI expression in AA might be caused by low serum IgE, indicating that IgE itself and not the type of allergic disorder determines FcεRI on DC subsets. Basophils were demonstrated to express FcεRI already with low serum IgE levels, whereas both DC subsets and especially the pDCs express FcεRI only at high serum IgE. This phenomenon might be caused by difference in composition of FcεRI. The β-chain, which is absent in FcεRI expressed on DCs, can amplify FcεRI cell surface expression.⁹ However, another hypothesis is that besides IgE, other factors such as cytokines or chemokines might be involved in the regulation of FcεRI expression on DCs. Interestingly, mDCs and pDCs express cutaneous lymphocyte antigen, a molecule involved in skin homing (data not shown). This implies that FcεRI-expressing blood DCs might be able to migrate to the skin and induce an immune response.

In conclusion, blood DCs from patients with AD and not patients with AA express increased levels of FcεRI, and this expression is correlated to serum IgE levels. Because pDCs have been reported to have tolerogenic properties,¹⁰ we hypothesize that FcεRI-expressing pDCs might have lost their tolerogenic capacity and may therefore be important in initiating an allergic response.

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